UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

OFFICE OF PESTICIDE PROGRAMS
REGISTRATION DIVISION (7505P)

August 25, 2011

**MEMORANDUM**

| | | |
|---|---|---|
| Subject: | Name of Pesticide Product: | HARTZ REFERENCE #134 |
| | EPA Reg. No. /File Symbol: | 2596-RAO |
| | DP Barcode: | DP 388572 |
| | Decision No.: | 445857 |
| | Action Code: | R310 |
| | PC Codes: | 128965 (Etofenprox: 55.0%) |
| | | 067501 (Piperonyl butoxide: 10.0%) |
| | | 057001 (N-octyl bicycloheptene dicarboximide: 1.0%) |
| | | 129032 (Pyriproxyfen: 0.5%) |
| | | 105402 (S-Methoprene: 0.25%) |

From: Byron T. Backus, Ph.D., Toxicologist
Technical Review Branch
Registration Division (7505P)

Byron T. Backus
August-25-2011
Marik Hasken, Ph.D.
Team Leader, Toxicology

To: Bonaventure Akinlosotu/Richard Gebken, RM 10
Insecticide Branch
Registration Division (7505P)

Registrant: THE HARTZ MOUNTAIN CORP.

FORMULATION FROM LABEL:

| Active Ingredient(s): | by wt. |
|---|---|
| 128965 Etofenprox | 55.0% |
| 067501 Piperonyl Butoxide | 10.0% |
| 057001 n-octyl bicycloheptene dicarboximide (MGK 264) | 1.0% |
| 129032 Pyriproxyfen (Nylar) | 0.5% |
| 105402 S-Methoprene | 0.25% |
| Other Ingredient(s): | 33.25% |
| TOTAL | 100.00% |

**ACTION REQUESTED:** The Risk Manager requests:

"For your review: MRID Nos. 484058-07, -10 for an R310. N/B: Same data pkg/studies applicable to 2596-RAT, RAI & RAO…"

**BACKGROUND:**

This package includes a companion animal safety study in adult beagles (MRID 48405807) and in 12 week old beagle puppies (MRID 48405810), a proposed label for 2596-RAO (which includes the statement not to use on dogs or puppies less than 12 weeks old or weighing less than 5 lbs), with claims (presumably indicative of the retreatment interval) for 28 day or 30 day or 1 month or 4 week efficacy. The label dosage rates are 0.031 fl. oz. (0.91 mL) for dogs and puppies weighing from 5 to 14 lbs, 0.066 fl. oz. (1.95 mL) for 15 to 30 lbs, 0.132 fl. oz. (3.90 mL) for 31 to 60 lbs, and 0.22 fl. oz. (6.5 mL) for >60 lbs. In addition, there are basic and alternate CSFs (both dated March 29, 2010).

**COMMENTS AND RECOMMENDATIONS:**

1. A contractor (Summitec Corporation) did the primary reviews and generated DERs for the two companion animal safety studies. TRB did the secondary reviews, and made revisions to the DERs as appropriate.

2. In both studies (MRIDs 48405807 and 48405810) the 1x dosage rate was 0.4 mL/kg. This is consistent with a dose of 0.91 mL for a dog or puppy weighing 5 lbs (=2.275 kg; 0.91 mL/2.275 kg = 0.4 mL/kg), and with the label statement not to use on dogs or puppies weighing less than 5 lbs.

3. In the adult dog study in MRID 48405807 no clinical signs of toxicity were observed. No treatment-related effects on body weight, body weight gain, food consumption or clinical pathology (hematology and clinical chemistry) parameters were reported.

   **It is concluded that the margin of safety in male and female adult beagle dogs administered TS#13345 [Etofenprox (56.65%), PBO (10.05%), MGK-264 (1.21%), Methoprene (2.43%), and Nylar (1.30%)] is at least 5x the recommended dose (0.40 mL/kg BW).**

   This companion animal safety study in male and female beagle dogs is classified as **Acceptable/Guideline** and **does satisfy** the guideline requirement for a companion animal safety study (OPPTS 870.7200) in the dog provided the specified retreatment interval is 30 days or more.

4. In the 12 week old puppy study in MRID 48405810 no treatment-related clinical signs of toxicity were observed. There were also no treatment-related effects on body weight, body weight gain, food consumption or clinical pathology (hematology and clinical chemistry) parameters.

   **It is concluded that the margin of safety in male and female puppies administered Dog Dermal Treatment B [Etofenprox (55.65%), Piperonyl butoxide (10.08%), MGK-264 (1.47%), Methoprene (3.12%) and Nylar (1.31%)] is at least 5x the recommended dose (0.40 mL/kg BW).**

   This companion animal safety study in male and female 12 week-old beagle puppies is **Acceptable/Guideline** and **does satisfy** the guideline requirement for a companion animal safety study (OPPTS 870.7200) in the dog provided the specified retreatment interval is 30 days or more.

5. TRB concludes that the two companion animal safety studies in MRIDs 48405807 and 48405810 adequately support the proposed use of 2596-RAO (HARTZ REFERENCE #134) in adult dogs

and 12 week old and older puppies weighing more than 5 lbs at the proposed dosage rates (0.031 fl. oz. [0.91 mL] for dogs and puppies weighing from 5 to 14 lbs, 0.066 fl. oz. [1.95 mL] for 15 to 30 lbs, 0.132 fl. oz. [3.90 mL] for 31 to 60 lbs, and 0.22 fl. oz. [6.5 mL] for >60 lbs).

6. Refer to the individual DERs for additional comments.

**DATA EVALUATION RECORD**
**TS#13345**
**(ETOFENPROX, PBO, MGK-264, METHOPRENE, NYLAR)**

**STUDY TYPE: COMPANION ANIMAL SAFETY - DOGS (OPPTS 870.7200)**
**MRID 48405807**

Prepared for
Registration Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202

Prepared by
Summitec Corporation
9724 Kingston Pike, Suite 602
Knoxville, Tennessee 37922

Task Order No. 3-C-02

| | | |
|---|---|---|
| Primary Reviewer:<br>Virginia A. Dobozy, V.M.D., M.P.H. | Signature:<br>Date: | Virginia Dobozy, AE<br>AUG 0 8 2011 |
| Secondary Reviewers:<br>Donna L. Fefee, D.V.M. | Signature:<br>Date: | Donna L Fefee, AE<br>AUG 0 8 2011 |
| Robert Ross, M.S., Program Manager | Signature:<br>Date: | Robert W. Ross<br>AUG 0 8 2011 |
| Quality Assurance:<br>Angie Edmonds, B.S. | Signature:<br>Date: | Angi Edmonds<br>AUG 0 8 2011 |

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

EPA Secondary Reviewer: Byron T. Backus, Ph.D.
Technical Review Branch, Registration Division (7505P)

Signature: Byron T. Backus
Date: August 25, 2011

EPA Tertiary Reviewer: Kit Farwell, D.V.M., D.A.B.T.
Risk Assessment Branch VII, Health Effects Division (7509P)

Signature: Kit Farwell
Date: 8/31/2011

Template version 02/06

## DATA EVALUATION RECORD

**STUDY TYPE:** Companion Animal Safety Study - Dogs; OPPTS 870.7200

**PC CODE:** 057001, 067501, 105402, 128965, 129032 **BARCODE:** 388568

**TEST MATERIAL (PURITY):** TS#13345 [Etofenprox (56.65%), PBO (10.05%), MGK-264 (1.21%), Methoprene (2.43%) and Nylar (1.30%)]

**TRADE NAME:** Not provided

**CITATION:** Slone, R.L. (2010) Safety of an experimental stripe-on administered topically to adult dogs. Professional Laboratory and Research Services, Inc., Corapeake, NC. PLRS 0933; Study No. Hartz 2120, March 16, 2010. MRID 48405807. Unpublished.

**SPONSOR:** The Hartz Mountain Corporation, Secaucus, NJ

**EXECUTIVE SUMMARY:** In a companion animal safety study (MRID 48405807), groups of six male and six female adult (336-392 days old on study day 0, 8.2-14.2 kg on day -1) beagle dogs were topically administered TS#13345 [Etofenprox (55.65%), Piperonyl butoxide (10.05%), MGK-264 (1.21%), Methoprene (2.43%) and Nylar (1.30%)] at doses of 1x, 3x and 5x the recommended dose of 0.40 mL/kg body weight (BW). A control group of six male and six female dogs received five applications of distilled water at 0.40 mL/kg BW. Another control group of six male and six female dogs received five applications of the product solvent at 0.14 mL/kg BW. The control or test material was applied using either a 3 mL or 6 mL syringe with no needle. The tip of the syringe was positioned on the dog's back between the shoulder blades and was used to separate the dog's hair so the material could be applied at the skin level. The contents of the syringe were applied to form a stripe from the shoulder blades to the base of the tail. To achieve the 3x and 5x doses, the control or test material was applied 3 or 5 times with 1 hour between the applications.

All animals survived to the end of the study. No clinical signs of toxicity were observed. No treatment-related effects on body weight, body weight gain, food consumption or clinical pathology (hematology and clinical chemistry) parameters were reported.

**It is concluded that the margin of safety in male and female adult beagle dogs administered TS#13345 [Etofenprox (56.65%), PBO (10.05%), MGK-264 (1.21%), Methoprene (2.43%), and Nylar (1.30%)] is at least 5x the recommended dose (0.40 mL/kg BW).**

This companion animal safety study in adult male and female beagle dogs is classified as **Acceptable/Guideline** and **does satisfy** the guideline requirement for a companion animal safety study (OPPTS 870.7200) in the dog provided the specified retreatment interval is 30 days or more.

**COMPLIANCE:** Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

## I. MATERIALS AND METHODS

### A. MATERIALS:

1. **Test materials:** TS#13345 [Etofenprox (56.65%), PBO (10.05%), MGK-264 (1.21%), Methoprene (2.43%) and Nylar (1.30%)]

2. **Solvent control:** TS#13334 (Solvent Control)

3. **Placebo control:** TS#13332 (Distilled water)

4. **Test animals:**

| | |
|---|---|
| **Species:** | Dog |
| **Strain:** | Beagle |
| **Age/weight** | On Day 0 – 336 to 392 days<br>On Day -1 – 8.2 to 14.2 kg |
| **Source:** | Ridglan Farms, Inc., Mt. Horeb, WI |
| **Housing:** | Individually housed in pens |
| **Diet:** | Purina Adult Dog Food, 200-400 g/day, depending on body weight |
| **Water:** | Not provided |
| **Environmental conditions:** | |
| **Temperature:** | Not provided |
| **Humidity:** | Not provided |
| **Air changes:** | Not provided |
| **Photoperiod:** | Not provided |
| **Acclimation period:** | Fourteen days |

### B. STUDY DESIGN:

1. **In life dates:** Start: December 1, 2009 (start of dosing); End: December 17, 2009 (last data collection).

2. **Animal assignment:** There were five groups in the study, each containing 12 dogs (6 males and 6 females), as shown in Table 1. Sixty-eight dogs were separated by gender and ranked from high to low based on body weights. Eight dogs (4 males and 4 females) were eliminated due to abnormal health during acclimation, low body weight or decreased appetite. The remaining dogs were then randomized to treatment groups by random draw by sexes. Five slips of paper, each with one of the letters of a group, were placed into a container and randomly drawn one at a time. The first letter drawn was assigned to the first male, the second letter to the second male and so forth until all letters had been drawn from the container. The slips were returned to the container and the procedure repeated until all the available dogs had been assigned to a treatment group. The female dogs were randomized in the same manner.

   The study was blinded to the laboratory performing the clinical pathology testing and the attending veterinarian to the treatment groups and to the technical staff to the 5x treatment groups.

**TABLE 1. Animal Assignment** [a]

| Group | Treatment | Number of Dogs | |
|---|---|---|---|
| | | Male | Female |
| A - 1X | TS#13345 – 1x recommended dose [a] | 6 | 6 |
| B - 3X | TS#13345 – 3x recommended dose | 6 | 6 |
| C - 5X | TS#13345 – 5x recommended dose | 6 | 6 |
| D - Solvent control | TS#13334 (solvent control) – 5x | 6 | 6 |
| E - Negative control | TS#13332 – (distilled water) – 5x | 6 | 6 |

[a] Data taken from p. 7, MRID 48405807.

[b] Recommended dose is 0.4 mL/kg BW.

3. **Dose selection rationale:** Doses were selected to meet the OPPTS 870.7200 guidelines. The study author stated that the normal recommended dose is 0.40 mL/kg without providing additional justification, such as citations for efficacy studies or range-finding studies.

4. **Preparation and treatment:** At each dosing, the control or test material was applied using either a 3 mL or 6 mL syringe with no needle. For groups A (1x), B (3x), C (5x) and E (distilled water control), a volume of 0.40 mL/kg BW was applied. For group D (solvent control), a volume of 0.14 mL/kg was applied. The tip of the syringe was positioned on the dog's back between the shoulder blades and was used to separate the dog's hair so the material could be applied at the skin level. The contents of the syringe were applied to form a stripe from the shoulder blades to the base of the tail. To achieve the 3x and 5x doses, the control or test material was applied 3 or 5 times with 1 hour between the applications.

5. **Statistics:**

   Body weight: The body weight and changes in body weight from baseline (Day -1) to each post-treatment assessment day (Days 7 and 14) were calculated for each group and summarized as descriptive statistics.

   Food consumption: The groups were compared with respect to the mean amount of food consumed with an Analysis of Variance (ANOVA) with a treatment effect across all groups. The percentage of dogs in each group which consumed all food offered was calculated. The

frequencies of the number of dogs which consumed all food were compared by a Chi-square test across all groups on each day.

Hematology and clinical chemistry: The individual hematology and clinical chemistry values on Days -1, 1, 7 and 14 (where applicable) were tabulated separately for each variable and each group using the following descriptive statistics: mean, standard deviation, coefficient of variation, geometric mean, median, maximum and number of observations in the group. The individual changes and percentage changes from baseline (Day -1) to each of the post-treatment days were calculated and tabulated for each variable and each group. The number of post-treatment values that fell outside of the reference range was calculated. The reference range was calculated as the minimum and maximum values of pre-treatment values on Day -1 across all groups. The post-treatment values were compared to the baseline values in an intra-treatment comparison by means of an ANOVA with the animal and observation time (baseline, post-treatment) as effects.

An inter-treatment comparison with respect to the change from baseline was also performed. The post-treatment values of the three test treatment groups (Groups A, B, C) were compared to each of the two control groups (Groups D and E) by means of an ANOVA with a treatment effect.

## C. METHODS:

### 1. Observations:

a. **General health observations:** The animals were observed twice daily for general health during the study. The observations constituted a cursory physical examination.

b. **Veterinary examinations:** A complete clinical exam was performed by a veterinarian on Day -1. On Day 0, the dogs were observed at approximately 1, 2, 3 and 4 hours post-treatment, beginning after the last treatment for each group and twice daily thereafter for the duration of the observation period. Any sign of an adverse reaction, including dermal irritation, was recorded.

2. **Body weight:** Animals were weighed on Days -8, -1, 7 and 14.

3. **Food consumption:** The dogs were offered approximately 200 to 400 g of food daily. Food consumption was recorded daily beginning on Day-7.

4. **Hematology and clinical chemistry:** Blood was collected for hematology and clinical chemistry assessments on the following study days: - 1, 1, 7 and 14 (for selected animals). Based on the results of Day 7, two dogs each from groups A and B, one dog each from groups C and D and three dogs from Group E were tested on Day 14. The animals were fasted prior to blood collection. The clinical pathology analyses were conducted by AniLytics, Inc., Gaithersburg, MD. The CHECKED (X) parameters were examined.

a. **Hematology:**

| | | | |
|---|---|---|---|
| X | Hematocrit (HCT)* | X | Leukocyte differential count* |
| X | Hemoglobin (HGB)* | X | Mean corpuscular HGB (MCH)* |
| X | Leukocyte count (WBC)* | X | Mean corpusc. HGB conc.(MCHC)* |
| X | Erythrocyte count (RBC)* | X | Mean corpusc. volume (MCV)* |
| X | Platelet count* | | Reticulocyte count |
| | Blood clotting measurements* | X | Heinz bodies |
| X | (Activated partial thromboplastin time) | | |
| | (Fibrinogen) | | |
| X | (Prothrombin time) | | |

*Recommended for companion animals safety evaluation based on OPPTS 870.7200

b. **Clinical chemistry:**

| | ELECTROLYTES | | OTHER |
|---|---|---|---|
| X | Calcium* | X | Albumin* |
| X | Chloride* | X | Creatinine* |
| | Magnesium | X | Urea nitrogen* |
| X | Phosphorus * | | Total Cholesterol |
| X | Potassium* (K) | X | Globulins* |
| X | Sodium* (NA) | X | Glucose* |
| | ENZYMES (more than 2 hepatic enzymes, eg., *) | X | Total bilirubin * |
| X | Alkaline phosphatase (AP)* | X | Total protein* |
| | Cholinesterase (ChE) | | Triglycerides |
| | Creatine kinase | | Albumin/Globulin ratio |
| X | Lactic acid dehydrogenase (LDH) | X | Direct bilirubin* |
| X | Alanine aminotransferase (ALT/also SGPT)* | | Indirect bilirubin |
| X | Aspartate aminotransferase (AST/also SGOT)* | | BUN/Creatinine ratio |
| X | Gamma glutamyl transferase (GGT) | | $TCO_2$ Bicarbonate |
| X | Amylase | | |
| | Sorbitol dehydrogenase | | |

* Recommended for a companion animal safety evaluation based on OPPTS 870.7200

5. **Urinalysis:** Urinalysis is not required for companion animal safety studies and was not done as part of the current study.

6. **Sacrifice and pathology:** There were no deaths or moribund sacrifices during the study. The study did not have a scheduled necropsy.

## II. RESULTS

A. **ACTUAL DOSES ADMINISTERED:** The mg/kg doses of active ingredients were not calculated.

B. **OBSERVATIONS:**

1. **Clinical signs of toxicity:** No treatment-related clinical signs of toxicity were observed. One dog in Group B (3x dose) had frothy, bloody vomit on Day 10 but this was not considered treatment-related.

2. **Application site examination:** Many dogs in the treated and solvent control group were noted to have wet, greasy, spiked, tacky or clumpy fur at the site of product application.

3. **Mortality:** All dogs survived to the end of the study.

C. **BODY WEIGHT AND WEIGHT GAIN:** Body weight data are presented in Table 2. During the treatment and observation period (Days -1 to 14), there was a dose-related decrease in mean body weight gain of the 3x and 5x treatment groups (Groups B and C) as compared to both the distilled water and solvent controls. These differences may have been partly attributable to the fact that increased numbers of animals in the 3x and 5x groups lost weight during Days -1 to 7 (8/12 and 11/12 5x animals, respectively) compared to the solvent and negative control groups (3/12 and 5/12 animals, respectively), while almost all of the animals on study gained weight during Days 7 to 14. Mean absolute body weights of the treated groups were similar to those of controls.

**TABLE 2. Body weight (kg) and body weight gain (kg) [a]**

| Group | Day -1 | Day 7 | Change Days -1 to 7 | Day 14 | Change Days -1 to 14 |
|---|---|---|---|---|---|
| A - 1X | 11.42±1.77 | 11.28±1.89 | -0.13±0.32 | 11.78±2.04 | 0.37±0.57 |
| B - 3X | 11.52±1.89 | 11.35±1.95 | -0.17±0.19 | 11.60±1.96 | 0.08±0.22 |
| C - 5X | 11.57±1.95 | 11.20±1.96 | -0.37±0.19 | 11.53±2.12 | -0.03±0.32 |
| D - Solvent control | 11.52±1.78 | 11.60±2.01 | 0.08±0.31 | 11.90±2.08 | 0.38±0.41 |
| E - Negative control | 11.35±1.96 | 11.32±1.96 | -0.03±0.19 | 11.72±2.10 | 0.37±0.24 |

[a] Extracted from pp. 22 and 565-574, MRID 48405807.

D. **FOOD CONSUMPTION:** There was no statistically significant difference in the mean food consumption on any day between Days -7 and 14. Food consumption (as measured by total amount of food consumed divided by total amount of food offered) was depressed in all 5 groups on days 0 (group ranges: 0.495 to 0.757) and 6 (group ranges: 0.325 to 0.621), with no indication of a dose response on either date. There was also no statistically significant difference between the groups in the percentage of dogs that consumed all their food.

E. **CLINICAL PATHOLOGY ANALYSES:**

1. **Hematology:** No treatment-related changes were observed. Slightly lower hemoglobin values were noted in Group B (3x) on Days 1 and 7 and in Group D (solvent control) on Day 1. Lower activated partial thromboplastin time was recorded for Groups A (1x) and D on Day 1. Lower neutrophil counts and higher lymphocyte counts were reported in Group B (3x). Since there was no dose response in any of these findings, they are not considered treatment-related.

2. **Clinical Chemistry:** There were no treatment-related effects.

## III. DISCUSSION AND CONCLUSIONS

A. **INVESTIGATORS' CONCLUSIONS:** The study author concluded that the test substance, TS#13345, produced no adverse clinical reactions at doses up to 5x the proposed dose when applied topically to adult male and female dogs.

B. **REVIEWER COMMENTS:** All animals survived to the end of the study. No clinical signs of toxicity were observed. Body weight gain from Days -1 to 14 in the 3x and 5x treatment groups was decreased in a dose-responsive manner, as compared to both the distilled water and solvent controls. Dogs of this age are expected to maintain their body weight over the course of such a short study; however, sporadic body weight losses are not uncommon in adult dogs. The magnitude of the decrease was minor, i.e., 0.08 kg and -.03 kg for the 3x and 5x groups, respectively, as compared to 0.38 kg and 0.37 kg for the distilled water and solvent controls, respectively, and differences of this magnitude could be due to the variability in the personnel and equipment used in weighing the animals. Therefore, the decreases are not considered treatment-related. No treatment-related effects on food consumption or clinical pathology (hematology and clinical chemistry) parameters were observed.

**It is concluded that the margin of safety in male and female adult beagle dogs administered TS#13345 [Etofenprox (56.65%), PBO (10.05%), MGK-264 (1.21%), Methoprene (2.43%), and Nylar (1.30%)] is at least 5x the recommended dose (0.40 mL/kg BW).**

This companion animal safety study in male and female beagle dogs is classified as **Acceptable/Guideline** and **does satisfy** the guideline requirement for a companion animal safety study (OPPTS 870.7200) in the dog provided the specified retreatment interval is 30 days or more.

C. **STUDY DEFICIENCIES:**

1. The mg/kg dose of active ingredients should have been calculated.

2. Draft labeling for Hartz Reference #134 accompanying the study contains multiple brand names but one list of active ingredients. The percentage of active ingredients differs from the test material used in the study, as shown in the table below. The percentages of Nylar and S-Methoprene were much higher in the test material. According to 870.7200(e)(2): "Because of the practice of combining several pesticides in one product, a procedure has been proposed whereby maximum concentrations of multiple active ingredients have been used to determine the margin of safety of end-use products. This practice has been referred to as the max/tox procedure."

| Ingredient | Draft label | Study test material |
|---|---|---|
| Etofenprox | 55% | 56.65% |
| Piperonyl butoxide | 10.0% | 10.05% |
| MGK-264 | 1.0% | 1.21% |
| Nylar | 0.5% | 1.30% |
| Methoprene | 0.25% | 2.43% |

3. The draft product labeling refers to "1st dose, 2nd dose, 3rd dose (xth) dose." According to the Companion Animal Safety Guideline, if the product label states that a treatment can be repeated at an interval of less than thirty days, the companion animal safety study should also include a repeat treatment. The study report should have included an explicit statement of the intended re-treatment interval.

4. The study report should have included an explicit statement that the solvent control group was given the inert ingredients at the same levels as in the end-use product.

5. The body weight and body weight gain data should have been summarized separately by sex to facilitate their interpretation.

**DATA EVALUATION RECORD**

**DOG DERMAL TREATMENT B**
**(ETOFENPROX, PIPERONYL BUTOXIDE,**
**MGK-264, METHOPRENE, NYLAR)**

**STUDY TYPE: COMPANION ANIMAL SAFETY - PUPPIES (OPPTS 870.7200)**
**MRID 48405810**

Prepared for
Registration Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202

Prepared by
Summitec Corporation
9724 Kingston Pike, Suite 602
Knoxville, Tennessee 37922

Task Order No. 3-C-01

| | | |
|---|---|---|
| Primary Reviewer:<br>Virginia A. Dobozy, V.M.D., M.P.H. | Signature:<br>Date: | Virginia D Dobozy, AE<br>AUG 0 8 2011 |
| Secondary Reviewers:<br>Donna L. Fefee, D.V.M. | Signature:<br>Date: | Donna Fefee AE<br>AUG 0 8 2011 |
| Robert Ross, M.S., Program Manager | Signature:<br>Date: | Robert H Ross<br>AUG 0 8 2011 |
| Quality Assurance:<br>Angie Edmonds, B.S. | Signature:<br>Date: | Angie Edmonds<br>AUG 0 8 2011 |

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

**EPA Secondary Reviewer: Byron T. Backus, Ph.D.**
**Technical Review Branch, Registration Division (7505P)**

Signature: Byron T. Backus
Date: August 25 2011

**EPA Tertiary Reviewer: Kit Farwell, D.V.M., D.A.B.T.**
**Risk Assessment Branch VII, Health Effects Division (7509P)**

Signature: Kit Farwell
Date: 8/31/2011

**Template version 02/06**

## DATA EVALUATION RECORD

**STUDY TYPE:** Companion Animal Safety Study - Puppies; OPPTS 870.7200

**PC CODES:** 057001, 067501, 105402, 128965, 129032 **BARCODE:** 388572

**TEST MATERIAL (PURITY):** Dog Dermal Treatment B [Etofenprox (55.65%), Piperonyl butoxide (10.08%), N-octyl bicycloheptene dicarboximide (MGK-264) (1.47%), Methoprene (3.12%) and Nylar (1.31%)]. Described as a clear yellow tinted liquid.

**TRADE NAME:** Not provided

**CITATION:** Doyle, V. (2010) Tolerance of an experimental flea and tick dermal treatment when topically administered to pups twelve weeks (84 to 90 days) old at 1x, 3x and 5x the recommended dose. Charles River Laboratories Preclinical Services Ireland, Ltd., Carrentrila, Ballina, Co. Mayo, Ireland. Laboratory Project ID USA004\09-001; Study No. Hartz 2119, April 19, 2010. MRID 48405810. Unpublished.

**SPONSOR:** The Hartz Mountain Corporation, Secaucus, NJ

**EXECUTIVE SUMMARY:** In a companion animal safety study (MRID 48405810), groups of six male and six female beagle pups, approximately 12 weeks (84-90 days) of age, were topically administered Dog Dermal Treatment B [Etofenprox (55.65%), Piperonyl butoxide (10.08%), MGK-264 (1.47%), Methoprene (3.12%) and Nylar (1.31%)] at doses of 1x, 3x and 5x the recommended dose of 0.40 mL/kg body weight (BW). A control group of six male and six female pups received five applications of distilled water at 0.40 mL/kg BW. Another control group of six male and six female pups received five applications of the product solvent at 0.14 mL/kg BW.

All animals survived to the end of the study. No treatment-related clinical signs of toxicity were observed. There were also no treatment-related effects on body weight, body weight gain, food consumption or clinical pathology (hematology and clinical chemistry) parameters.

**It is concluded that the margin of safety in male and female puppies administered Dog Dermal Treatment B [Etofenprox (55.65%), Piperonyl butoxide (10.08%), MGK-264 (1.47%), Methoprene (3.12%) and Nylar (1.31%)] is at least 5x the recommended dose (0.40 mL/kg BW).**

This companion animal safety study in male and female 12 week-old beagle puppies is **Acceptable/Guideline** and **does satisfy** the guideline requirement for a companion animal safety study (OPPTS 870.7200) in the dog provided the specified retreatment interval is 30 days or more.

**COMPLIANCE:** Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

## I. MATERIALS AND METHODS

### A. MATERIALS:

1. **Test materials:** Dog Dermal Treatment B [Etofenprox (55.65%), Piperonyl butoxide (10.08%), N-octyl bicycloheptene dicarboximide (MGK-264)(1.47%), Methoprene (3.12%) and Nylar (1.31%)]

2. **Solvent control:** Solvent Control B [redacted]

3. **Placebo control:** Distilled water

4. **Test animals:**

| | |
|---|---|
| **Species:** | Dog |
| **Strain:** | Beagle |
| **Age/weight** | On Day 0 - males: 84-90 days old; females: 84-89 days old<br>On Day -2 – males: 1.5 – 5.8 kg; females: 2.0 – 4.9 kg |
| **Source:** | Charles River Laboratories Preclinical Services Ireland Ltd. |
| **Housing:** | Individually housed in pens |
| **Diet:** | Country Select Puppy Food (Cambrian Pet Foods Limited), approximately 400 g/puppy/day |
| **Water:** | Tap water, *ad libitum* |
| **Environmental conditions:** | |
| **Temperature:** | 17 - 20° C |
| **Humidity:** | 35 - 64% |
| **Air changes:** | Not provided |
| **Photoperiod:** | Not provided |
| **Acclimation period:** | Fourteen days |

### B. STUDY DESIGN:

1. **In life dates:** Start: November 18, 2009; End: March 3, 2010

2. **Animal assignment:** There were five groups in the study, each containing 12 pups (6 males and 6 females), as shown in Table 1. On Study Day -2, all pups that met the study inclusion criteria were ranked within sex in order of decreasing body weight. When pups were of the same body weight, they were ranked in order of decreasing animal number. Due to the unavailability of sufficient pups for a single set, the study was run in 8 sets. Male and females pups in each set were listed in replicates of five consecutively-ranked pups as possible. Within each replicate, one pup was assigned to each of the five study groups using random order numbers derived from Fisher and Yates tables. Incomplete sets were assigned similarly. Table 2 lists the number of pups in each set. The study was not blinded.

**TABLE 1. Animal assignment** [a]

| Group | Treatment | Number of Pups | |
|---|---|---|---|
| | | Male | Female |
| 1 - Negative control | Distilled water control (5 applications at the rate of 0.4 mL/kg BW) | 6 | 6 |
| 2 - Vehicle control | Solvent control (5 applications at rate of 0.14 mL/kg BW) | 6 | 6 |
| 3 - 1X | Test item – 1x (1 application at rate of 0.40 mL/kg BW) | 6 | 6 |
| 4 - 3X | Test item – 3x (3 applications of 0.40 mL/kg BW) | 6 | 6 |
| 5 - 5X | Test item – 5x (5 applications of 0.40 mL/kg BW | 6 | 6 |

[a] Data taken from page 23, MRID 48405810.

**TABLE 2. Number of animals per set** [a]

| Group | Set | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| 1 - Negative control | - | 2 M, 2 F | - | 1 M, 2 F | 1 F | 1 M, 1 F | 2 M | - |
| 2 - Vehicle control | 1 F | 1 M, 1 F | - | 1 M, 2 F | - | 3 M, 2 F | 1 M | - |
| 3 - 1X | 1 M, 1 F | 1 F | 1 F | 1 M, 1 F | 1 M | 2 M, 1 F | - | 1 M, 1 F |
| 4 - 3X | 1 M | 2 F | - | 1 M, 2 F | 1 M | 1 M, 1 F | 1 M | 1 M, 1 F |
| 5 - 5X | - | 1 M, 2 F | 1 M, 1 F | - | 1 M, 1 F | 2 M, 1 F | - | 1 M, 1 F |

[a] Tabulated by the reviewer from Table 1, page 39, MRID 48405810.
M = male; F = female

The puppies ranged in age from 84 to 90 days of age on Day 0. The proposed label for Hartz® Reference #134 (EPA File Symbol 2596-RAO) includes the statement: "Use only on dogs or on puppies 12 weeks of age or older."

| TABLE 3. Ages of puppies on day 0 [a] | | |
|---|---|---|
| Group | Age range (days) | Mean age ± S.D. (days) |
| 1 - Negative control – males | 85 – 90 | 88.17 ± 2.14 |
| 1 - Negative control – females | 84 – 89 | 87.33 ± 2.25 |
| 2 - Vehicle control - males | 85 – 90 | 87.17 ± 2.40 |
| 2 - Vehicle control - females | 85 – 89 | 86.50 ± 1.97 |
| 3 - 1X – males | 84 – 89 | 86.00 ± 2.00 |
| 3 - 1X - females | 84 – 89 | 87.00 ± 2.10 |
| 4 - 3X – males | 84 – 90 | 87.00 ± 2.61 |
| 4 - 3X - females | 85 – 89 | 86.83 ± 1.72 |
| 5 - 5X – males | 84 – 89 | 86.00 ± 2.37 |
| 5 - 5X - females | 84 – 89 | 86.50 ± 2.26 |

[a] Calculated by the reviewer from Table 1, page 39, MRID 48405810.

It is concluded that the Agency can accept the use of this product on puppies 12 weeks old and older.

3. **Dose selection rationale:** Doses were selected to meet the OPPTS 870.7200 guidelines. The study author stated that the normal recommended dose is 0.40 mL/kg without providing additional justification, such as citations for efficacy studies or range-finding studies.

4. **Preparation and treatment:** At each dosing, either the control or test material was applied using a syringe with no needle. For groups 1 (distilled water), 3 (1x), 4 (3x) and 5 (5x), a volume of 0.40 mL/kg BW was applied. For group 2 (solvent control), a volume of 0.14 mL/kg was applied. The target volumes were rounded up to the nearest 0.1 mL. The tip of the syringe was positioned on the pup's back between the shoulder blades and was used to separate the pup's hair so the material could be applied at the skin level. The contents of the syringe were applied to form a stripe from the shoulder blades to the base of the tail. Syringes were not weighed before or after administration, but syringe volumes were visually confirmed immediately pre- and post-administration. To achieve the 3x and 5x doses, the control or test material was applied 3 or 5 times with 1 hour (± 5 minutes) between the applications. There was evidence of run-off at each dosing with the distilled water control.

5. **Statistics:** Statistical analyses were performed on body weight, hematology and clinical chemistry parameters and food consumption using a mixed model repeated measures analysis of covariance including set and its interaction with day as random effects and sex, (treatment) group, sampling day and the interactions: group*day, group*sex and sex*day and group*sex*day as fixed effects. The covariate of each variable was the applicable baseline measurement. For body weight, the average of the study days -14, -2 and 0 were used. For hematology and clinical chemistry parameters, the day -1 values were used. For food consumption, the average of day -8 to day 0 values were used.

For each analysis, the appropriate variance-covariance matrix structure was selected from among compound symmetry, heterogeneous compound symmetry, first-order autoregressive, heterogeneous first-order autoregressive and unstructured based on Akaike Information Criterion.

If the three-way interaction group*sex*day was significant at $\alpha$=0.05, then the statistical analysis was considered inconclusive and comparisons between treatment group were made based on descriptive statistics.

If the three-way interaction group*sex*day was not significant at $\alpha$=0.05, then the two-way interaction group*sex was evaluated. If this was significant at $\alpha$=0.05, then the statistical analysis was considered inconclusive and comparisons between treated groups must be based on descriptive statistics.

If the group*sex*day and group*sex interactions were not significant, then two-way interaction group*day was evaluated. If this was significant at $\alpha$=0.05, pairwise comparisons of means of groups 2-5 against group 1 for each study day were tested. These pairwise comparisons were obtained from linear contrasts on the day by treatment group interaction.

If the group*sex*day, group*sex and group*day interactions were not significant, the treatment main effect was evaluated. If this term was significant, treatment contrasts comparing the means of groups 2-5 against group 1 were tested at the 5% significance level.

The adequacies of all statistical models were checked by analyzing the residuals. Data transformations were applied as appropriate.

The statistical hypotheses being tested were that there was no difference between the treatment groups. All tests were two-sided and were performed at the unadjusted 5% level of significance. Each animal randomized to a treatment group and for which there were any relevant data was included in the statistical analyses. All analyses were performed using SAS®/STAT (SAS® Version 9.1.3).

## C. METHODS:

### 1. Observations:

c. **General health observations:** The animals were observed twice daily for general health from Study Day -14 to Study Day -1. If the technician carrying out the general health observations considered the animal abnormal, a veterinarian was contacted to perform an examination.

d. **Veterinary examinations:** Veterinary examinations were conducted on all animals prior to the first treatment and at 1 hour (±5 minutes), 2 hours (±10 minutes), 3 hours (±10 minutes) and 4 hours (±10 minutes) after the final treatment on Study Day 0. In addition, clinical assessments were performed by a veterinarian twice daily on all pups assigned to all groups from Study Day 1 to Study Day 14, inclusive, once in the morning and once in the afternoon, with at least four hours between assessments. The veterinarian scored the following parameters as either present (score "1") or absent (score "0"): lethargy, ataxia, recumbency, paralysis, coma, pruritis, hyperactivity, tremors, convulsions, abnormal mydriasis, abnormal miosis, corneal opacity, dyspnea, tachypnea, coughing, abnormal salivation, vomiting, abnormal

mucous membranes, ocular discharge, nasal discharge, cardiovascular changes, abnormal feces, abnormal urine, abnormal coat condition, abnormal site of stripe-on application. For each score of "1", a description of the condition was made at the first point of detection.

2. **Body weight:** Animals were weighed on Days -14, -2, 0, 7 and 14.

3. **Food consumption:** Pups were offered approximately 400g/pup of food daily. The pups were fed once daily in the afternoon between 12:00 and 15:00. From Study Day -7 to Study Day 14, diet not consumed from the previous day was removed from the pup's pen and weighed, except on the days when the animals were fasted for blood sampling.

4. **Hematology and clinical chemistry**: Blood was collected for hematology and clinical chemistry assessments on the following study days: - 1, 1 [at +24 hours (±2 hours post first dosing)], and 7. If there were missing values or abnormalities detected in an animal at Day 7, blood samples were taken from that pup on Study Day 14 for a measurement of the affected parameter. Five animals in total were sampled on Study Day 14. Blood was collected following an overnight fast of at least 10 hours. The CHECKED (X) parameters were examined.

   a. **Hematology:**

| | | | |
|---|---|---|---|
| X | Hematocrit (HCT)* | X | Leukocyte differential count* |
| X | Hemoglobin (HGB)* | X | Mean corpuscular HGB (MCH)* |
| X | Leukocyte count (WBC)* | X | Mean corpusc. HGB conc.(MCHC)* |
| X | Erythrocyte count (RBC)* | X | Mean corpusc. volume (MCV)* |
| | Platelet count* | | Reticulocyte count |
| | Blood clotting measurements* | | |
| X | (Activated partial thromboplastin time) | | |
| | (Fibrinogen) | | |
| X | (Prothrombin time) | | |

*Recommended for companion animals safety evaluation based on OPPTS 870.7200

b. **Clinical chemistry:**

| | ELECTROLYTES | | OTHER |
|---|---|---|---|
| X | Calcium* | X | Albumin* |
| X | Chloride* | X | Creatinine* |
| | Magnesium | X | Urea nitrogen* |
| X | Phosphorus * | | Total Cholesterol |
| X | Potassium* (K) | X | Globulins* |
| X | Sodium* (NA) | X | Glucose* |
| | ENZYMES (more than 2 hepatic enzymes, eg., *) | X | Total bilirubin * |
| X | Alkaline phosphatase (AP)* | X | Total protein* |
| | Cholinesterase (ChE) | | Triglycerides |
| | Creatine kinase | | Albumin/Globulin ratio |
| | Lactic acid dehydrogenase (LDH) | X | Direct bilirubin* |
| X | Alanine aminotransferase (ALT/also SGPT)* | | Indirect bilirubin |
| X | Aspartate aminotransferase (AST/also SGOT)* | | BUN/Creatinine ratio |
| | Gamma glutamyl transferase (GGT) | | $TCO_2$ Bicarbonate |
| | Amylase | | |
| | Sorbitol dehydrogenase | | |

* Recommended for a companion animal safety evaluation based on OPPTS 870.7200

5. **Urinalysis:** Urinalysis is not required for companion animal safety studies and was not done as part of the current study.

6. **Sacrifice and pathology:** There were no deaths or moribund sacrifices during the study. The study did not have a scheduled necropsy.

## II. RESULTS

A. **ACTUAL DOSES ADMINISTERED:** The mg/kg doses of active ingredients were not calculated.

B. **OBSERVATIONS:**

1. **Clinical signs of toxicity:** No treatment-related clinical signs of toxicity were observed. On occasion, pups in both the control and treated groups had abnormal feces, sometimes containing blood and/or mucus, but there was no dose-related effect. Several animals in both the treated and control groups were observed to have hematomas around the jugular area, probably due to the blood collection.

2. **Application site examination:** Changes in the hair coat, including clumping, matting, greasy appearance, spiking and deposits were observed in all animals in Groups 2 (except for one), 3, 4 and 5 on Study Day 0 until Study Day 2.

3. **Mortality:** All pups survived to the end of the study.

C. **BODY WEIGHT AND WEIGHT GAIN:** Body weight data are presented in Table 3. No treatment-related effects on body weight were observed. Body weight gain during the treatment period (Days 0-7, 7-14, and 0-14) was comparable between the control and treated groups.

| TABLE 4. Mean body weight (kg) and body weight gain (kg) | | | | | | | |
|---|---|---|---|---|---|---|---|
| Group | Sex | Body weight [a] | | | | | Body weight gain [b] |
| | | Day -14 | Day -2 | Day 0 | Day 7 | Day 14 | Day 0 to 14 |
| 1 - Negative control | M | 3.68±1.39 | 3.88±1.24 | 3.93±1.17 | 4.03±1.15 | 4.23±1.19 | 0.30 |
| | F | 3.03±0.59 | 3.37±0.49 | 3.43±0.49 | 3.67±0.41 | 3.85±0.40 | 0.42 |
| 2 - Vehicle control | M | 3.47±0.68 | 3.68±0.59 | 3.75±0.58 | 3.90±0.63 | 4.02±0.62 | 0.27 |
| | F | 2.58±0.74 | 3.00±0.55 | 3.02±0.58 | 3.20±0.67 | 3.45±0.69 | 0.43 |
| 3 - 1X | M | 3.30±1.31 | 3.48±1.12 | 3.55±1.12 | 3.67±1.11 | 3.82±1.13 | 0.27 |
| | F | 3.30±0.60 | 3.62±0.58 | 3.62±0.53 | 3.68±0.58 | 3.78±0.56 | 0.16 |
| 4 - 3X | M | 3.95±0.51 | 4.20±0.48 | 4.22±0.48 | 4.37±0.36 | 4.52±0.31 | 0.30 |
| | F | 3.37±0.92 | 3.62±0.81 | 3.63±0.79 | 3.85±0.86 | 4.03±0.83 | 0.40 |
| 5 - 5X | M | 3.95±0.99 | 4.22±0.90 | 4.25±0.89 | 4.42±0.83 | 4.58±0.75 | 0.33 |
| | F | 3.53±0.51 | 3.82±0.40 | 3.78±0.34 | 3.97±0.34 | 4.17±0.25 | 0.39 |

[a] Data extracted from Table 1, page 7 of 122 (Statistical Report), MRID 48405810.

[b] Calculated by the reviewer.

M = male; F = female

D. **FOOD CONSUMPTION:** No treatment-related effects were reported. Most of the pups ate the entire ration on most days. There were slight reductions in mean food consumption on Study Days -2, 0 and 6; these reductions tended to be more pronounced in females. From p. 17 of MRID 48405810: "Diet was withdrawn from all animals, between 16:00 and 17:00 on the afternoon of Study Days -2, 0 and 6, in order to facilitate fasting prior to blood sampling..." Otherwise, "...diet not consumed from the previous day was removed from each pup's pen between 10:00 and 12:00..." It is noteworthy that Group 5 (5x test item) male puppies all consumed their entire ration on day 0 (the day of treatment) and on day 6 as well.

| TABLE 5. Mean food consumption ± S.D. (g) on selected days | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | Sex | | | | | | | | |
| | | Day -3 | Day -2 | Day -1 | Day 0 | Day 1 | Day 5 | Day 6 | Day 7 |
| 1- Negative control | M | 389.7±18.7 | 338.0±74.8 | 383.8±41.6 | 369.2±79.9 | 383.8±42.5 | 395.0±17.2 | 309.2±103.5 | 394.2±18.2 |
| | F | 385.3±38.4 | 332.3±86.0 | 392.7±21.9 | 319.7±70.8 | 386.0±24.3 | 401.8±1.2 | 354.0±74.9 | 384.7±40.0 |
| 2-Vehicle control | M | 401.7±1.5 | 372.7±44.4 | 401.2±0.8 | 349.3±83.3 | 391.0±26.0 | 402.0±1.3 | 383.3±44.3 | 401.3±0.8 |
| | F | 352.0±55.9 | 255.0±144 | 345.7±116.7 | 295.5±133.6 | 360.2±77.3 | 379.0±56.8 | 302.5±86.7 | 387.3±19.7 |
| 3 - 1X | M | 365.3±57.4 | 401.2±1.0 | 375.7±32.5 | 337.5±103.6 | 387.2±36.3 | 386.0±37.2 | 325.3±118.6 | 376.2±38.5 |
| | F | 371.8±41.1 | 280.8±115.6 | 383.2±45.2 | 302.7±151.9 | 372.2±59.6 | 344.5±89.2 | 312.0±100.8 | 401.2±1.5 |
| 4 - 3X | M | 402.0±0.9 | 367.2±52.8 | 401.7±1.0 | 401.0±0.9 | 378.7±52.7 | 396.5±12.0 | 348.2±82.6 | 401.5±1.0 |
| | F | 379.3±52.6 | 371.5±71.8 | 377.5±57.1 | 353.8±83.5 | 388.2±32.9 | 378.5±56.1 | 324.2±97.7 | 401.5±1.0 |
| 5 - 5X | M | 401.7±0.8 | 380.2±51.5 | 401.8±0.8 | 401.3±0.8 | 392.7±19.4 | 401.5±1.0 | 401.7±1.2 | 401.7±1.0 |
| | F | 402.0±0.9 | 325.7±86.4 | 401.5±1.0 | 383.8±43.5 | 400.5±0.5 | 401.7±0.8 | 371.5±73.7 | 401.3±0.8 |

[a] Data extracted/calculated from Table 5, page 94 of MRID 48405810.

## E. CLINICAL PATHOLOGY ANALYSES:

1. **Hematology:** No treatment-related changes were observed. All treated groups had lower eosinophil counts on Study Day 7 as compared to the distilled water control. This finding is not considered clinically significant or treatment-related. Lower lymphocyte counts in the 1x and 3x groups are also not considered treatment-related.

2. **Clinical Chemistry:** No treatment-related effects were reported.

## III. DISCUSSION AND CONCLUSIONS

A. **INVESTIGATORS' CONCLUSIONS:** The study author concluded that the results of the study show that the experimental flea and tick dermal treatment, Dog Dermal Treatment B, when administered topically to pups twelve weeks (84 to 90 days) old at 1x, 3x and 5x the recommended dose is well tolerated both locally and systemically.

B. **REVIEWER COMMENTS:** All animals survived to the end of the study. No clinical signs of toxicity were observed. No treatment-related effects on body weight, body weight gain, food consumption or clinical pathology (hematology and clinical chemistry) parameters were observed.

**It is concluded that the margin of safety in 12 week old male and female puppies administered Dog Dermal Treatment B [Etofenprox (55.65%), Piperonyl butoxide (10.08%), MGK-264 (1.47%), Methoprene (3.12%) and Nylar (1.31%)] is at least 5x the recommended dose (0.40 mL/kg BW).**

This companion animal safety study in male and female 12 week-old beagle puppies is **Acceptable/Guideline** and **does satisfy** the guideline requirement for a companion animal safety study (OPPTS 870.7200) in the dog provided the specified retreatment interval is 30 days or more.

## C. STUDY DEFICIENCIES:

1. There was an unequal representation of the control and treated groups in the replicates. Only two sets (2 and 6) had all groups represented. Two sets (3 and 8) had no control animals. Since there were no treatment-related effects in the study, this deficiency does not invalidate the study results.

2. The mg/kg dose of active ingredients should have been calculated.

3. Draft labeling for Hartz #134 accompanying the study contains multiple brand names but one list of active ingredients. The percentage of active ingredients differs from the test material used in the study, as shown in the table below. The percentage of Nylar and S-methoprene in the Dog Dermal Treatment B used in the study was much higher than listed on the proposed product label.

| Ingredient | Draft label | Study test material | |
|---|---|---|---|
| | | Nominal | Actual |
| Etofenprox | 55% | 55% | 55.65% |
| Piperonyl butoxide | 10.0% | 10% | 10.08% |
| MGK-264 | 1.0% | 1% | 1.47% |
| Nylar | 0.5% | 1% | 1.31% |
| S-methoprene | 0.25% | 2.3% | 3.12% |

4. The study report and label should have included an explicit statement of the intended re-treatment interval. However, the data will support a 28-day retreatment interval.

5. The study report should have included an explicit statement that the solvent control group was given the inert ingredients at the same levels as in the end-use product.

These deficiencies do not negate the acceptability of this study.

1. **DP BARCODE:** 388572
2. **PC CODES:** 128965 (Etofenprox: 55.0%); 067501 (Piperonyl butoxide: 10.0%); 057001 (N-octyl bicycloheptene dicarboximide: 1.0%); 129032 (Pyriproxyfen: 0.5%); 105402 (S-Methoprene: 0.25%)
3. **CURRENT DATE:** August 24, 2011
4. **TEST MATERIAL:** TS#13345 [Etofenprox (56.65%), PBO (10.05%), MGK-264 (1.21%), Methoprene (2.43%), and Nylar (1.30%); used in MRID 48405807]; Dog Dermal Treatment B [Etofenprox (55.65%), Piperonyl butoxide (10.08%), N-octyl bicycloheptene dicarboximide (MGK-264) (1.47%), Methoprene (3.12%) and Nylar (1.31%)]. Described as a clear yellow tinted liquid. [Used in MRID 48405810].

| Study/Species/Lab<br>Study # / Date | MRID | Results | Tox. Cat. | Core Grade |
|---|---|---|---|---|
| Companion Animal Safety Study (adult dog)/336-392 day old beagles/Professional Laboratory and Research Services, Inc., Corapeake, NC/PLRS 0933/March 16, 2010 | 48405807 | 3 groups (each 6M & 6F) of adult beagles were treated at 1x, 3x, 5x the recommended dose of 0.4 mL/kg on day 0. A control group of 6M & 6F received five applications of 0.4 mL distilled water/kg, while another control group received five applications of the product solvent at 0.14 mL/kg. No clinical signs of toxicity were observed and there were no treatment-related effects on body weight, body weight gain, food consumption or clinical pathology (hematology and clinical chemistry). Study is acceptable provided the specified retreatment interval is 30 days or more. | N/A | A |
| Companion Animal Safety Study (beagle puppies)/84-90 days old on Day 0/Charles River Preclinical Services, Ireland Ltd./Lab Project ID USA004\09-001/April 19, 2010 | 48405810 | Groups of 6M & 6F beagle puppies (~12 weeks of age) received topical applications at 1x, 3x, and 5x the 0.4 mL dose level. A control group of 6M & 6F received five applications of distilled water at 0.4 mL/kg while another group of 6M & 6F received 5 applications of the product solvent at 0.14 mL/kg. No treatment-related signs of toxicity were observed. There were also no treatment-related effects on body weight, body weight gain, food consumption or clinical pathology (hematology and clinical chemistry) parameters. Study is acceptable provided the specified retreatment interval is 30 days or more. | N/A | A |

Core Grade Key: A = Acceptable, S = Supplementary, U = Unacceptable, W = Waived